This Month in *The Journal*

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C3ORF60 Mutations Cause Complex I Deficiency

Saada et al., page 718

Complex I is one of five multiprotein complexes that make up the oxidative phosphorylation (OXPHOS) system. The OXPHOS system resides within the mitochondria and is responsible for the conversion of nutrients to ATP. When a part of this process is dysfunctional, patients are severely affected and often die in early childhood. Mutations in one of the many genes that make up complex I are the most frequent cause of OXPHOS disorders. Complex I is made up of at least 45 components, and about half of the cases of complex I deficiency have been attributed to mutations that affect the function or assembly of complex I. In an effort to establish the etiology of the remaining cases of complex I deficiency, researchers previously performed comparative genomics studies to predict which other genes might play an important role in this complex. Here, Saada and colleagues analyze one of these genes, *C3ORF60*, in five patients with complex I deficiency from three families. The authors identify three different mutations that are predicted to disrupt the structure or interactions of the protein. Complementation analysis reveals that the wild-type protein is able to correct severe complex I deficiency in patient fibroblasts. The authors also perform localization and interaction studies to establish the function of C3ORF60 and to determine how the protein interacts with other components of the complex. They demonstrate that C3ORF60 is required for proper complex I assembly and OXPHOS function.

An Improved Human mtDNA Molecular Clock

Soares et al., page 740

A molecular, or genetic, clock relates the number of genetic differences between two species to the evolutionary timeframe of development and change within the evolving genome. This analysis can therefore provide useful information regarding human genetic history. Previous molecular mtDNA clocks have assumed a linear mutation rate over evolutionary history without taking genetic selection into consideration. In addition, many analyses focus on a partial mtDNA sequence. Here, Soares and colleagues introduce a method for calibrating the mtDNA mutation rate and use this method to adjust the mtDNA molecular clock. They focus their analysis on the entire mtDNA genome, including both the control and coding regions. In addition to supporting a nonlinear model of mutation accumulation, their study supports previous research using mitochondrial DNA (mtDNA) and showing Africa to be the origin of all human mtDNA. Because their analysis takes the timing of human settlement of different regions of the world into account and uses the chimpanzee-human split as a reference, Soares et al. provide a modified timescale for the out-of-Africa dispersal with the L3 haplotype dating back ~70 kiloyears and the M, N, and R haplogroups dating back 50–70 kiloyears. Furthermore, their method for calculating genomic mutation rates may have a broader application outside of human mtDNA.

XCI in Human Pre-Implantation Embryos

van den Berg et al., page 760

Normal females and males have two copies of each somatic chromosome and differ at the chromosomal level only in that females have two X chromosomes and males have one X and one Y chromosome. The manner in which females handle the excess of information contained within these two Xs has been a matter of research for many years. Studies have shown that X chromosome inactivation (XCI), in which one copy of the two X chromosomes is turned off in each cell, is the mechanism that female mammals use to compensate for the extra X. In mice, imprinting leads to XCI of the paternal X starting at the 4 cell stage prior to implantation and persists until reactivated in the inner cell mass. This is followed by random XCI in somatic mouse cells. The process of XCI in humans is less well understood, and the timing of XCI has remained an unresolved issue. Here, van den Berg and colleagues re-examine this matter. Through careful examination of human female preimplantation embryos, the authors find evidence of XCI by the 8 cell stage. This timing correlates well with the timing of genome activation in humans. These data suggest that the mechanism and timing of X chromosome dosage compensation is evolutionarily conserved in placental mammals.

CNVs on 17q24.2-q24.3 and Hypertrichosis

Sun et al., page 807

Congenital generalized hypertrichosis (CGH) is a disease in which patients have abnormal hair growth all over their bodies. CGH is sometimes seen as part of a syndrome and

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can also be part of congenital generalized hypertichosis terminalis (CGHT) with or without gingival hyperplasia. This rare condition has fascinated people for centuries, but although a number of loci have been mapped, the underlying genetic cause for CGHT has not yet been identified. Here, Sun et al. study three Chinese families in which CGHT is inherited in a dominant fashion. Their linkage scan identifies a region on chromosome 17, and subsequent analysis suggests that a microdeletion might be etiologic. Each family is found to carry a different overlapping genomic microdeletion. In addition, a sporadic Chinese patient with CGHT is found to have a microduplication in the same locus. The authors discuss the four genes that reside in the overlapping region of these genomic alterations and make additional suggestions about the possible positional effects that the rearrangements could be exerting.

Origin of Europeans: mtDNA Evidence Suggests an Italian Source

Pala et al., page 814

After the initial widespread colonization of Europe, human populations significantly altered their range as they migrated southward during the extreme conditions of the last glacial maximum. The locations where people congregated during this time are called refugia, and their isolation led to a decrease in genetic variation as a result of drift and founder effects. Once the weather conditions moderated, people began to move more north once more; their distribution patterns have been followed via analysis of mtDNA and y-chromosome haplogroups in modern European populations. Evidence suggests that the source of a large proportion of the repeopling came from the Franko-Cantabrian, Balkan, and Ukranian refuge zones. Pala and colleagues wanted to know whether humans from a fourth refuge, one that was located on the Italian peninsula, also contributed to the postglacial repopulation of Europe. The authors start by studying a branch of an ancient mtDNA haplogroup that is found at a high frequency on the island of Sardinia. An analysis of the haplotype diversity of related branches in modern Europeans suggests that the Italian refuge was the source of the postglacial expansion of these people. In southern France, the authors also find mtDNA samples that are similar to those of Sardinia and suggest that the ancient obsidian trade between the two regions led to this link.